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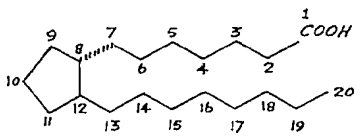
(54) PROSTAGLANDIN CONTAINING COMPOSITIONS

(71) We, SCHERING AKTIENGESELLSCHAFT, a Body Corporate organised according to the laws of Germany, of Berlin and Bergkamen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with prostaglandin containing compositions, especially prostaglandin containing freeze dried powders suitable for the production of aqueous solutions or solid galenical preparations for enteral, parenteral and topical application, and also with a process for the manufacture of freeze dried powders containing a prostaglandin.

Prostaglandins are hydroxy-fatty acids that are derived from the basic skeleton of prostanoic acid:



Prostanoic acid.

As prostaglandins there are to be understood prostaglandins that occur in nature and synthetic analogues of natural prostaglandins, for example those known from the literature.

Natural prostaglandins are, for example, prostaglandins of the A_1, A_2, E_1, E_2, E_3, $F_{1\alpha}$, $F_{2\alpha}$, B_1, B_2, D_1 and D_2 series.

PGE_2, for example, has a cis-5,6-double bond, a trans-13,14-double bond, a C-9 keto group and an α-hydroxyl group in each of the 11- and 15-positions of prostanoic acid.

Synthetic analogues of the natural prostaglandins are, for example, carboxylic acid esters and amides at C-1 of 19-oxa-, 17-substituted-ω-tris-nor- and 16-substituted-ω-tetra-nor-prostaglandins. Furthermore, for example, the hydroxyl groups in the 9- and/or 11- and/or 15-position(s) may be etherified or esterified, and/or a 15-hydroxyl group may be oxidized to the keto group and ketalised. The double bonds in the 10,11- or 13,14-position may be methylenated or hydrogenated.

Prostaglandins are of great interest on account of their remarkable biological and pharmacological properties. It has been known, however, that prostaglandins, especially prostaglandin E-derivatives, are relatively unstable. There has been no lack of attempts to stabilize prostaglandins by means of suitable carrier materials.

Solutions of prostaglandins in methanol, depending on the pH-value in the case of PGE_1 and PGE_2, are stable at room temperature for up to 40 days [Eur. J. Pharmacol. 4 (1968) 416—420]. Methanolic solutions, however, have no medicinal use owing to the toxicity of methanol.

Solutions of PGE_2 in absolute ethanol keep for at least 6 months at −20°C [Amer. J. Hosp. 30 (1973) 236—239]. Solutions in ethanol are also unsuitable for medicinal use, as such solutions must be diluted with water or other carrier substances before use.

According to a report in Lipids 8, 10 (1973) 592—594 PGE_2 in ethanol at 4°C loses 5—12% of its activity in one month, and PGE_2 decomposes so rapidly in sodium chloride solution that after 15 days only 58—62% of the original activity remains.

In United States Patent Specification No. 3,826,823 there have been described prostaglandin preparations that are stabilized with polyvinylpyrrolidone. According to a preferred method the prostaglandin material and polyvinylpyrrolidone are dissolved in methylene dichloride and evaporated at 50°C *in vacuo*. The dry powder obtained from the film or pharmaceutical preparations produced therefrom can be kept for 8 months at room temperature. As 10 to 1000 parts of polyvinylpyrrolidone are required for 1 part of prostaglandin, the prostaglandin, material to be formulated is already highly diluted. Accordingly, it is not possible according to the process of this United States Patent Specification to obtain highly concentrated prostaglandin preparations.

The present invention is based on the problem of preparing a prostaglandin containing freeze dried powder that is stable for a long time and is suitable, for example, for the preparation of aqueous solutions and solid galenical preparations.

This problem has now been solved in accordance with the present invention by using as a stabilizing agent tris(hydroxymethyl)-aminomethane hydrochloride.

The present invention accordingly provides a composition comprising a prostaglandin and tris(hydroxymethyl) - aminomethane hydrochloride and, if desired, an inert filler. The composition is advantageously in the form of a powder that has been freeze dried, such a powder being suitable for the production of preparations for enteral, parenteral or topical application in human or veterinary medicine. Such a freeze dried powder is stable for a long time at room temperature and especially at 4°C, and may be stored in a suitable airtight vessel, for example a sealed ampoule or a sealed multiphial.

The present invention also provides a process for the manufacture of a prostaglandin containing powder, wherein a prostaglandin and tris(hydroxymethyl) - aminomethane and, if desired, an inert filler are dissolved in a solvent, the solution is adjusted with hydrogen chloride to a pH-value within the range of from 5 to 7, the solution is filtered and the resulting solution is freeze dried.

The prostaglandin used in the compositions and in the process of the present invention may be a naturally occurring prostaglandin or a synthetic analogue of a naturally occurring prostaglandin, and may be, for example, a prostaglandin of the E series, for example the E_2 series.

It is found that the addition of tris(hydroxymethyl) - aminomethane hydrochloride brings about a considerable improvement in the stability of the prostaglandin material. For example, the prostaglandin containing freeze dried powders forming a preferred embodiment of the compositions of the present invention are stable at 4°C for longer than 1 year.

If, for example, prostaglandin E_2 is freeze dried, without the addition of tris(hydroxymethyl)-aminomethane hydrochloride, from an aqueous-alcoholic solution a decomposition of more than 30% is found in the course of three weeks at room temperature.

If there are added to the aqueous-alcoholic prostaglandin E_2 solution the pharmaceutically usual buffers, with the exception of tris(hydroxymethyl) - aminomethane hydrochloride, rapid decomposition of the freeze dried prostaglandin E_2 also occurs. Thus, after freeze drying, the decomposition of the prostaglandin E_2 at room temperature takes place completely in the course of 12 days with the addition of a sodium citrate/citric acid buffer at a pH value of 3.5, and the degree of decomposition at room temperature is 15% in the course of one week with the addition of a triethanolamine/hydrochloric acid buffer at a pH-value of 7.0, 30% in the course of two weeks with the addition of a disodium hydrogen phosphate/citric acid buffer at a pH-value of 5.6, and 10% in the course of two weeks with the addition of a disodium hydrogen phosphate//citric acid buffer at a pH-value of 5.1 and polyvinylpyrrolidone.

On the other hand, the stability of prostaglandin E_2 in freeze drying is, surprisingly, considerably improved by the addition of tris(hydroxymethyl) - aminomethane hydrochloride.

As prostaglandins are substances having a very strong action, it is usual to administer only very small quantities of a prostaglandin. It is therefore advantageous for the freeze dried powders included within the scope of the present invention, as is technically usual, to contain inert fillers, for example polyvinylpyrrolidone, sorbitol, mannitol, lactose, cyclodextrins and glycine. These substances are usually added in freeze drying in order to obtain a preparation having a fine highly porous structure, which imparts to the dry preparation a high rate of solution when dissolving it in water or a physiological sodium chloride solution (for example, when preparing preparations to be used for intravenous injection). In accordance with the present invention polyvinylpyrrolidone is preferably used as inert filler.

As the solvent in the process of the present invention there may be used water or a mixture of water with a readily volatile solvent miscible with water. Such readily volatile solvents miscible with water are, for example, ethanol, acetone and dioxan.

The ratio of the prostaglandin to the tris(hydroxymethyl) - aminomethane hydrochloride and, if present, the filler used in the compositions and process of the present invention may vary within wide limits. As some prostaglandins are more stable than others the quantity of the stabilizing agent, tris(hydroxymethyl) - aminomethane hydrochloride, added depends also on the stability of the prostaglandins. In the case of unstable prostaglandins larger quantities of tris(hydroxymethyl) - aminomethane hydrochloride are used, and to the extent to which they are more stable smaller quantities are used. The ratio is, *inter alia*, also dependent on the finally desired concentration of prostaglandin in the form of the application finally desired. For example, for each 1 part of prostaglandin there may be used 1 to 1000, and preferably 1 to 200, parts of tris(hydroxymethyl)-aminomethane hydrochloride and also 0 to 1000, and preferably 1 to 200, parts of an inert filler, for example polyvinylpyrrolidone, the parts being by weight.

The compositions of the present invention

may be in the form of pharmaceutical preparations suitable for administration to a human being or in the form of preparations suitable for veterinary use.

Thus, for example, the freeze dried powders of the present invention (which may be prepared in accordance with the process of the present invention) may be worked up with suitable auxiliary substances into a large number of human or veterinary medicinal preparations, which are suitable for enteral, parenteral or topical use. Thus, solutions for injection or infusion may be prepared from the powders with a physiological sodium chloride solution. With solid auxiliary substances, for example mannitol, lactose, maize starch, magnesium stearate or talcum, there can be obtained from the powders, for example, tablets, powders and capsules.

The present invention also includes within its scope a pack which comprises (i) a physiologically tolerable composition comprising a prostaglandin and tris(hydroxymethyl) - aminomethane hydrochloride together with (ii) instructions for the use of the composition in veterinary medicine.

The following Examples illustrate the invention:—

Example 1

The composition of a prostaglandin E_2 solution used for freeze drying, per ampoule:

1.0 mg of prostaglandin E_2,
7.5 mg of tris(hydroxymethyl) - aminomethane and
5.0 mg of polyvinylpyrrolidone,

adjusted with 0.1N- and 0.01N-hydrochloric acid to a pH-value of 5.0, and made up to 0.5 ml with bidistilled water.

Method of preparation:

The prostaglandin E_2 was brought into solution by being added to an ice-cold solution of the polyvinylpyrrolidone and the tris-(hydroxymethyl)-aminomethane in distilled water. By the cautious addition of 0.1N- and 0.01N-hydrochloric acid with further strong cooling the pH-value of the solution was adjusted to 5.0. The solution was then made up to the necessary volume. After filtration through a membrane filter the solution was measured out into ampoules. The solution was frozen by immersing the ampoules in an acetone/dry ice freezing mixture, and was immediately freeze dried in a pre-cooled freeze drying apparatus for about 48 hours. When the freeze drying had been completed the ampoules were immediately sealed.

Example 2

The composition of a prostaglandin solution used for freeze drying, per ampoule:

2.0 mg of (5Z,13E) - (8R,11R,12R,15S) - 11,15 - dihydroxy - 9 - oxo - 5,13 - prostadienoic acid (N-methane sulphonylamide),
15.0 mg of tris(hydroxymethyl) - aminomethane and
10.0 mg of polyvinylpyrrolidone,

adjusted to a pH-value of 5.0 with 0.1N- and 0.01N-hydrochloric acid, and made up to 1.0 ml with bidistilled water.

The preparation was carried out as described in Example 1.

Example 3

The composition of a prostaglandin solution used for freeze drying, per ampoule:

0.05 mg of 16 - phenoxy - prostaglandin - E_2 methane sulphonamide,
7.50 mg of tris(hydroxymethyl - aminomethane, and
5.00 mg of polyvinylpyrrolidone,

adjusted with 0.1N- and 0.01N-hydrochloric acid to a pH-value of 5.0, and made up to 0.5 ml with bidistilled water.

The preparation was carried out as described in Example 1.

The dry preparations manufactured as described in Examples 1 to 3 were stored at 4°C with the exclusion of light.

The freeze drying may be carried out in other suitable vessels, for example multiphials.

WHAT WE CLAIM IS:—

1. A composition comprising a prostaglandin and tris(hydroxymethyl)-aminomethane hydrochloride.

2. A composition as claimed in claim 1, wherein the prostaglandin is a prostaglandin of the E series.

3. A composition as claimed in claim 2, wherein the prostaglandin is a prostaglandin of the E_2 series.

4. A composition as claimed in any one of claims 1 to 3, wherein the tris(hydroxymethyl)-aminomethane hydrochloride is present in an amount within the range of from 1 to 1000 parts per one part present of the prostaglandin, the parts being by weight.

5. A composition as claimed in claim 4, wherein the tris(hydroxymethyl) - aminomethane hydrochloride is present in an amount within the range of from 1 to 200 parts per one part present of the prostaglandin, the parts being by weight.

6. A composition as claimed in any one of claims 1 to 5, which also contains an inert filler.

7. A composition as claimed in claim 6, wherein the inert filler is polyvinylpyrrolidone.

8. A composition as claimed in claim 6 or 7, wherein the inert filler is present in an

amount up to 1000 parts per one part of the prostaglandin, the parts being by weight.

9. A composition as claimed in claim 8, wherein the inert filler is present in an amount within the range of from 1 to 200 parts per one part of the prostaglandin, the parts being by weight.

10. A composition as claimed in any one of claims 1 to 9, which is in the form of a powder that has been freeze dried.

11. A composition as claimed in any one of claims 1 to 9, which is in the form of a powder that has been freeze dried, the powder being contained in an air-tight vessel.

12. A composition as claimed in claim 11, wherein the air-tight vessel is a sealed ampoule.

13. A composition as claimed in claim 11, wherein the air-tight vessel is a sealed multiphial.

14. A composition as claimed in any one of claims 1 to 9, which is in the form of a pharmaceutical preparation suitable for administration to a human being.

15. A composition as claimed in any one of claims 1 to 9, which is in the form of a preparation suitable for veterinary use.

16. A composition as claimed in claim 14 or 15, which is in a form suitable for enteral, parenteral or topical administration.

17. A composition as claimed in claim 14 or 15, which is in the form of a solution suitable for administration by injection or infusion.

18. A composition as claimed in claim 14 or 15, which is in the form of a powder, tablet or capsule.

19. A composition as claimed in claim 1 substantially as described in Example 1 or 2 herein.

20. A composition as claimed in claim 1 substantially as described in Example 3 herein.

21. A pack which comprises (i) a physiologically tolerable composition comprising a prostaglandin and tris(hydroxymethyl)aminomethane hydrochloride together with (ii) instructions for the use of the composition in veterinary medicine.

22. A process for the manufacture of a prostaglandin containing powder, wherein a prostaglandin and tris(hydroxymethyl)-aminomethane are dissolved in a solvent, the solution is adjusted with hydrogen chloride to a pH-value within the range of from 5 to 7, the solution is filtered and the resulting solution is freeze dried.

23. A process as claimed in claim 22, wherein the prostaglandin is a prostaglandin of the E series.

24. A process as claimed in claim 23, wherein the prostaglandin is a prostaglandin of the E_2 series.

25. A process as claimed in any one of claims 22 to 24, wherein the solvent is water.

26. A process as claimed in any one of claims 22 to 24, wherein the solvent is a mixture of water and a readily volatile solvent miscible with water.

27. A process as claimed in claim 26, wherein the readily volatile solvent is ethanol, acetone or dioxan.

28. A process as claimed in any one of claims 22 to 27, wherein the tris(hydroxymethyl) - aminomethane is used in such an amount that the tris(hydroxymethyl) - aminomethane hydrochloride formed therefrom with the hydrogen chloride is present in an amount within the range of from 1 to 1000 parts for each part used of the prostaglandin, the parts being by weight.

29. A process as claimed in claim 28, wherein the tris(hydroxymethyl) - aminomethane is used in such an amount that the tris(hydroxymethyl) - aminomethane hydrochloride formed therefrom with the hydrogen chloride is present in an amount within the range of from 1 to 200 parts for each part used of the prostaglandin, the parts being by weight.

30. A process as claimed in any one of claims 22 to 29, wherein an inert filler is also dissolved in the solvent.

31. A process as claimed in claim 30, wherein the inert filler is polyvinylpyrrolidone.

32. A process as claimed in claim 30 or 31, wherein the inert filler is used in an amount up to 1000 parts for each part used of the prostaglandin, the parts being by weight.

33. A process as claimed in claim 32, wherein the inert filler is used in an amount within the range of from 1 to 200 parts for each part used of the prostaglandin, the parts being by weight.

34. A process as claimed in any one of claims 22 to 33, wherein after the freeze drying the resulting powder is introduced into a vessel which is then sealed.

35. A process as claimed in claim 34, wherein the vessel is an ampoule.

36. A process as claimed in claim 34, wherein the vessel is a multiphial.

37. A process as claimed in claim 22, conducted substantially as described in Example 1 or 2 herein.

38. A process as claimed in claim 22, con-

ducted substantially as described in Example 3 herein.

39. A prostaglandin containing powder whenever made by the process claimed in any one of claims 22 to 38.

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